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Toward A General Synthesis of Chlorins

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Abstract

Recently we described a new synthesis of C,D-ring symmetric chlorins **11**, involving 2+2 condensation of *bis*-formyl-dihydrodipyrrins **9** with symmetrically substituted dipyrromethane diacids **10** (*Method I*). However, while versatile in many aspects, *Method I* was unsuited to the broader goal of synthesizing fully non-symmetric chlorins of general structure **15**, which requires regioselective control over the reacting centers in the A,B- and C,D-ring components. In this paper we describe four new 2+2 strategies that accomplish this differentiation (*Methods II-V*). Of these, *Method V*, which combines operational simplicity with moderate to high product yields, proved to be the most effective route, exploiting reactivity differences between the two formyl groups of A,B-rings **9** to impart excellent regioselectivity. *Methods II-IV* are also useful alternatives to *Method V*, although in some cases the appropriately functionalized precursors are less readily available. All four approaches generate single regioisomers of diversely substituted chlorins, and in every case the 2+2 condensation is accomplished in a simple, one-flask procedure without need for additives such as oxidizing agents or metals. Taken together, these methodologies provide expanded access to an array of chlorins for SAR studies that may advance the effectiveness of PDT and other applications.

Introduction

The chlorins are a class of 18π-electron aromatic tetrapyrroles, formally derived by saturation of the C2-C3 bond in ring A of porphyrins (see below). The most ubiquitous members of this class belong to the chlorophyll *a* (**1**) group of chromophores, the primary photoreceptors in photosynthesis in higher plants, algae, cyanobacteria, and other microorganisms.[1] Although far less abundant than **1**, other chlorins play crucial roles in both terrestrial and marine organisms. Among these, bonellin (**2**) is the hormone responsible for sexual differentiation in larvae of the echiuran worm *Bonella viridis*,[2] and cyclopheophorbide (**3**) is representative of several closely related chlorins believed to inhibit oxidative damage in certain marine invertebrates.[3] Other pheophorbides show promising anti-tumor activity.[3c]

"Non-natural" chlorins are also of considerable chemical and biological interest, in part because of their "tunable" photophysical properties. Owing to this capability they have come under increasing scrutiny as key components in various light-mediated applications, ranging from alternative energy sources to medicine. Light-energy conversion techniques have received particular attention, encompassing such topics as *(1)* the creation of artificial photosynthetic systems;[4] *(2)* design of molecular wires or antenna arrays;[4f,5] *(3)* production of hydrogen as an alternative fuel;[4e,6] and *(4)* generation of electricity with chlorin-based solar cells.[7] Synthetic chlorins are also being studied for applications in materials science[8] and medical imaging.[9] Finally, in the medical field, chlorins are emerging as more effective "second generation" photosensitizers in photodynamic therapy (PDT), a treatment method that employs visible light to trigger phototoxic reactions that eradicate malignant tissue or infections.[10] While PDT is an established and effective means of treating certain cancers, there

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are many lesser known but increasingly important applications.[11] Of particular note, PDT shows great promise in combating infectious disease, including antibiotic-resistant strains of bacteria.[12]

Most naturally occurring chlorins bear a full complement of substituents on the pyrrolic rings and have an asymmetric substitution pattern.[1] The nature and position of these substituents can have a dramatic effect on the spectral properties of the chromophore and can affect the functions of biologically active chlorins.[13] Furthermore, the ability to control substituent placement may be crucial to the successful use of synthetic chlorins in many applications, including multi-chlorin arrays.[14] Despite this importance, the selective assembly of fully substituted, unsymmetrical chlorins remains a significant challenge.

The majority of *de novo* chlorin syntheses build upon the pioneering work of Battersby and Montforts, involving either photochemical or base-induced cyclization of tetrapyrroles **4** to afford chlorins of general structure **5** (Scheme 1).[15] This strategy has been employed in the syntheses of numerous naturally occurring and "non-natural" chlorins, and it played a prominent role in early studies on vitamin B_{12} biosynthesis.[16] It is not without shortcomings, however. Principally these relate to the limited choice of methodology for preparing tetrapyrroles **4** and the generally inefficient nature of the macrocyclization step (~20-72% yields).[15,17] In addition, the photochemical process is only practical on very small scales. In a noteworthy variant of this approach, Lindsey et al. have shown that condensation of fragments **6** and **7**, followed by oxidative cyclization employing Zn as a template, provides Zn-chlorins **8** in 7-45% yields (often this sequence can be performed in a single reaction vessel with only slightly lower yields).[13a,14,18] As in the Battersby/Montforts strategies, though, a limiting factor in this approach is the availability of precursors of type **6** and **7**, in particular with respect to synthesizing more highly substituted derivatives.[13a,14,19] Finally, while numerous other strategies for synthesizing chlorins have been devised, a truly general approach remains elusive.[20]

Recently we described a new synthetic approach to C,D-symmetric chlorins of general structure **11**, involving acid-catalyzed condensation of A,B-ring dialdehydes **9** and C,D-ring dipyrromethanes **10** (*Method I*, Scheme 2).[21] An attractive feature of this approach is that the cyclodehydration of **9** and **10** leads directly to the thermodynamically stable, aromatic chlorin nucleus **11**, with no need for oxidation state adjustment[18] or double bond isomerization(s).[20a] Consequently, the experimental conditions are straightforward, requiring no metal template and only routine precautions against air and light. Also, there is considerable flexibility in setting substituents about the periphery of the macrocycle. In one investigation, for example, *Method I* was employed in the synthesis of a diversely substituted series of twenty-five chlorins **11** designed to probe substituent effects on depth of cell membrane penetration in PDT (38-85% yields).[21b] However, while versatile in many aspects, in its present form *Method I* is unsuited to the broader goal of synthesizing unsymmetrical chlorins, which requires regioselective control over the four reacting carbon atoms in **9** and **10**. To address this limitation we have been exploring variations of this "2+2" condensation strategy that incorporate the desired level of selectivity, four of which are described below (*Methods II-V*).

Results and Discussion

Syntheses of Unsymmetrical Chlorins via a "2+2" Strategy

Method II—Any "2+2" approach to unsymmetrical chlorins requires that the reactive sites of the A,B-and C,D-rings be differentiated, such that a single regioisomer is generated. The first strategy we tested for meeting this criterion is outlined in Scheme 3, in which the differentiating step involves mild acid-catalyzed condensation of C-9 protected A,B-ring precursors of type **12** with readily available[22] C-11 protected C,D-ring precursors **13** (*Method II*). Our

supposition was that *seco*-chlorins **14** would afford chlorins **15** upon decarboxylative formylation, with the stipulation that *mono*-formylation is followed by rapid cyclodehydration as opposed to oligomerization. As precedent for this approach, porphyrins have been prepared by a similar method in fair yields (30-35%),[23] although in these examples post-cyclization oxidation was required to give the aromatic macrocycles. In the analogous cyclization of **14**, the aromatic chlorin would be obtained directly upon cyclodehydration (cf. **16**→**15**), with the same advantages as described above for *Method I*. In particular, aromatization would drive forward any equilibrium processes.

To explore this route we prepared a group of three A,B-ring substrates **12a-c**, employing methodology closely analogous to that earlier developed for synthesizing diformyl-dihydropyrrins **9** (Scheme 4). As described previously,[24] dihydrodipyrrins **21** were derived in three steps, on scales ranging up to several grams, by *(1)* Pd(0)-mediate coupling-cyclization of alkyne acids **17** with iodopyrrole **18** to afford enelactones **19** (74-98%); *(2)* methylenation of the lactone carbonyl group with Petasis's reagent (**19**→**20**; 86-92%); and *(3) in situ* enol-ether hydrolysis/amination (**20**→**21**; 71-82%). The desired A,B-ring aldehydes **12a-c** were then obtained directly from **21** by selenium dioxide oxidation of the C-20 methyl group (65-81%).

Our initial investigations using *Method II* were conducted with the A,B-ring substrate **12a** and unsymmetrical C,D-ring substrate **13a**, and provided encouraging results. Thus, decarboxylation of **13a** with *p*-toluenesulfonic acid (TsOH) in CH_2Cl_2/MeOH afforded an 84% yield of the C-19 unsubstituted dipyrromethane **22**, which on coupling with **12a** in the presence of $TiCl_4$ gave a 66% yield of the moderately stable tetrapyrrole **14a** (*path a*, Scheme 5). Next, dissolution of **14a** in neat TFA, followed shortly thereafter by dilution with CH_2Cl_2 and excess triethyl orthoformate (TEOF), gave a 50% yield of the desired chlorin **15a** as a single regioisomer. The substitution pattern of **15a** was unequivocally established by NOE studies (see Supporting Information), as well as by direct comparison with its subsequently prepared regioisomer **26** (*vide infra*).

Having established proof-of-concept, we were hopeful that the transformation of **13a** to **15a** could be streamlined to a "single pot" procedure, by-passing the isolation of the α-unsubstituted dipyrromethane **22** and *seco*-chlorin **14a**. There was precedent for this possibility in our original studies on C,D-symmetric chlorins (cf. Scheme 2), where we found that dipyrromethane dicarboxylic acids **10** and dialdehydes **9** underwent acid-catalyzed condensation under conditions where *t*-butyl ester cleavage is exceedingly slow (5% TFA/CH_2Cl_2). The initial step of this goal, avoiding isolation of **22**, was readily accomplished by treating a solution of dipyrromethane **13a** and aldehyde-ester **12a** in CH_2Cl_2 with sufficient neat TFA to bring the final concentration to 5% (*path b*, Scheme 5). After stirring ~1 h at rt under Ar, the anticipated *seco*-chlorin **14a** was isolated in 68% yield. Cyclization of **14a** as before then provided a route to chlorins that circumvented the separate $TiCl_4$-catalyzed condensation of **22** and **12a**. Next, a second simplification was realized by effecting the TFA-initiated condensation and cyclization steps in a single flask without isolation of intermediate **14a** (*path c*). In this modification, a solution of **13a** and **12a** in 5% TFA/CH_2Cl_2 was stirred at rt under Ar for a period of 5 h, when it appeared that formation of **14a** was complete.[25] The resulting deep purple reaction was then adjusted to a concentration of 20% TFA/CH_2Cl_2 by addition of neat TFA and then treated with excess trimethyl orthoformate. After stirring an additional 16 h at rt, chlorin **15a** was isolated in 34% yield by straightforward concentration and chromatography. This yield compares favorably with the overall yields of 28% and 34% obtained following *paths a* and *b* respectively, and in no case was evidence found for formation of regioisomeric chlorin products.[26]

To test the generality and effectiveness of *Method II*, we synthesized two additional unsymmetrical chlorins **15b,c**, and for comparison, three C,D-ring symmetric chlorins **15d-f** previously prepared by *Method I* (Table 1; cf. also Scheme 2). We observed little effect of non-*meso* C,D-ring substituents *f* on the course of these syntheses. However, the nature of the A,B-ring *meso*-substituents R had a significant influence on reaction efficiency, with dihydrodipyrrins **12a** (R=Me) and **12b** (R=Ph) affording considerably higher yields of the corresponding chlorins **15a,d** and **15b,e** than the case with unsubstituted substrate **12c** (R=H). These results are consistent with a reaction pathway involving cationic intermediates stabilized by electron donating substituents at C-5. Interestingly, *Method II* proved to be less efficient than *Method I* for synthesizing C,D-ring symmetric chlorins of type **15d-f**, yields in each case being significantly lower. However, even with these limitations, *Method II* does provide access to unsymmetrical chlorins via the readily available precursors **12** and **13**.

Most of our efforts at optimizing *Method II* centered on the decarboxylative formylation process leading from tetrapyrroles **14** to presumed chlorin intermediates **16** (cf. Scheme 3), which we had reason to believe might be problematic. In particular, the initial step in such transformations involves *ipso*-protonation (or formylation) on the carboxyl-bearing pyrrole ring, followed by re-aromatization with loss of CO_2.[27] Consequently, acid-catalyzed decarboxylation (or decarboxylative formylation) of electron deficient pyrroles is typically very slow.[28] In the present case, tetrapyrrole **14** is a vinylogous amidine presumably favoring N-protonation in ring A or D, either of which lowers the likelihood of *ipso*-electrophilic attack on rings B or C. Indeed, in earlier mechanistic studies we observed the same phenomenon with dihydrodipyrrins having a basic pyrroline ring nitrogen.[21b] Since this step in *Method II* could not be optimized further, we examined three additional approaches to unsymmetrical chlorins that avoided decarboxylative formylation on basic ring systems (*Methods III-V*, Scheme 6). *Methods III* and *IV* achieve regioselectivity in similar fashion to *Method II*, except that in both cases a formyl group is incorporated in the C,D-ring fragment. In contrast, *Method V* employs the same *bis*-formyl A,B-ring precursor **9** previously utilized in our syntheses of C,D-ring symmetric chlorins (*Method I*, cf. Scheme 2), regioselectivity being dictated by the far greater reactivity of the formyl group in ring A.

Method III—Our synthetic design for *Method III* is similar in concept to *Method II* (cf. Schemes 3 and 5), except the aldehyde destined to become C-10 is incorporated early on (Scheme 6). To test this approach, model aldehyde-acid **23** was synthesized from the known dipyrromethane **24**,[29] by a two step sequence consisting of decarboxylative formylation (in this case routine) followed by benzyl ester hydrogenolysis (Scheme 7). The next step called for mild acid-catalyzed condensation of **23** with the A,B-ring precursor **12a**, followed by *t*-butyl ester hydrolysis and cyclodehydration. Each of these steps had close precedent in *path c* of *Method II* (cf. Scheme 5), although self-condensation of **23** was a potential complication. Blank experiments, however, indicated that side reactions of this nature could be controlled. In the event, condensation of **12a** and **23** in 5% TFA/CH_2Cl_2, followed by adjustment to 25% TFA/CH_2Cl_2, afforded chlorin **15a** in 28% yield, with no evidence for byproducts arising from self-condensation (Scheme 6). During this sequence a polar intermediate was observable by TLC, whose crude NMR spectrum was consistent with the anticipated tetrapyrrole condensation product of **12a** and **23**. However, several attempts at isolating and fully characterizing this compound were unsuccessful, making further optimization difficult. Thus, while clearly a viable means of synthesizing unsymmetrical chlorins, *Method III* had no advantages over *Method II* in terms of simplicity or effectiveness.

Method IV—*Method IV* constituted a relatively minor variation on *Method III*, substituting a *t*-butyl ester in C,D-ring precursor **25** for the carboxylic acid blocking group employed in **23** (Scheme 6). We were also interested in preparing the regioisomeric chlorin **26** to compare directly with the chlorin **15a** synthesized previously using both *Method II* and *III*. The synthesis

of **25** was simplified by the fact that it could be prepared from the same dipyrromethane precursor **24** previously employed in the synthesis of C,D-ring precursor **23** (Scheme 7). In the case of **25**, benzyl ester hydrogenolysis and decarboxylation of **24** were effected first, followed by formylation under very mild Vilsmeier-Haack conditions to ensure that the *t*-butyl ester remained intact.[30]

As in the analogous step in *Method III*, self-condensation of C,D-ring precursor **25** was a potential complication in *Method IV*, in particular under the more strongly acidic conditions required for *t*-butyl ester cleavage (25% TFA/CH_2Cl_2). However, we were again confident that the far more electrophilic C-20 formyl group in ring A of **12a** would react preferentially. A second point worth noting pertains to the *t*-butyl ester group at C-9 in ring B. While we fully expected this group to undergo concomitant ester cleavage, we had previously found that decarboxylation in such ring systems is sluggish, due to the electron withdrawing effect of the protonated pyrroline ring A.[21b] This argument formed the basis for regiochemical control in the condensation of **12a** and **25** and for avoiding self condensation of A,B-ring precursor **12a**. Thus, we expected that relatively rapid deprotection of C-19, followed by condensation with the highly reactive C-20 aldehyde, would afford a bilin intermediate that is properly disposed for ring closure to the corresponding chlorin. This turned out to be the case, as stirring of **12a** and **25** in 25% TFA/CH_2Cl_2 for 24 h provided chlorin **26** in 39% yield (*Method IV*, Scheme 6). Direct comparison of chlorins **26** and **15a** then demonstrated conclusively that there had been no crossover in regiochemical control in *Methods II-IV*. While this result was satisfying, evidence was accumulating that an even more straightforward approach to unsymmetrical chlorins was feasible employing diformyl ring-A,B precursors **9** (*Method V*).

Method V—In our previous chlorin studies we demonstrated that diformyl derivatives **9** are excellent A,B-ring precursors for synthesizing C,D-symmetric chlorins **11** (cf. Scheme 2).[21] We had assumed, though, that these materials lacked the unambiguous differentiation at C-10 and C-20 necessary to impart regioisomeric selectivity. The validity of this assumption was now called into question, based upon the substantial reactivity differences we had uncovered between pyrrole- and pyrroline-type formyl groups (*vide supra*). Thus, it now seemed clear that electron rich pyrroles would undergo selective condensation with the more reactive pyrroline aldehyde found on ring A in **9**, as opposed to the vinylogous amide-like formyl group present in ring B. This approach was first tested with dialdehyde **9a** and dipyrromethane **13a**, which were stirred together for 5 h at rt in 5% TFA/CH_2Cl_2 to effect decarboxylation at C-19 and initial condensation. After stirring an additional 16 h in 25% TFA/CH_2Cl_2. *chlorin **15a** was isolated in 74% yield without any effort at optimization*.[31] Furthermore, this methodology proved to be quite general. Both C,D-ring symmetric and unsymmetrically substituted chlorins were accessible by this route, with yields ranging from 22-87% (Table 2). As can be seen, the C-5 *meso*-substituent still exerted some influence on the reaction efficiency, with the trend mirroring that previously noted for *Method II*. That is, *meso*-H derivatives **15c,f,i** were consistently formed in lower yields than the corresponding *meso*-Me or *meso*-Ph chlorins, again suggesting the intermediacy of cationic species. Importantly, however, the yields of *all* chlorins were significantly improved over those obtained by *Method II*, including the *meso*-H series which were brought into a preparatively useful range (note that the 22% yield for **15i** is atypically low, even for *meso*-H substituted derivatives). Finally, direct comparison of *Methods I* and *V* was possible for the series of C,D-ring symmetric chlorins **15d-f**. In these examples the yields for *meso*-Me and *meso*-phenyl chlorins **15d,e** were somewhat higher employing *Method V* (78% and 73%, respectively; vs 73% and 60% for *Method I*), presumably due to better control over competing oligomerization. Interestingly, though, *meso*-H chlorin **15f** did not follow this trend, and was better prepared using *Method I* (38% vs 63%).

Conclusion

In summary, we have built upon our 2+2 synthesis of C,D-ring symmetric chlorins to develop four new strategies for the preparation of chlorins that are fully asymmetric in their substitution pattern. *Method V*, which combines operational simplicity with moderate to high product yields, proved to be the most effective route, with reactivity differences between the two formyl groups of A,B-rings **9** imparting excellent regioselectivity. *Methods II-IV* are also useful alternatives to *Method V* if the appropriately functionalized precursors are readily available. All four approaches generate single regioisomers of diversely substituted chlorins, and in every case the 2+2 condensation is accomplished in a simple, one-flask procedure without need for additives such as oxidizing agents or metals. Taken together, these methodologies provide expanded access to an array of chlorins for SAR studies that may advance the effectiveness of PDT and other applications.

Experimental Section

Representative procedures for the syntheses of chlorins by *Methods II-V*

2,2,5,7,8,12, 13,18-octamethylchlorin-17-propionic acid methyl ester (15a)

Method II: A solution of **12a** (10.1 mg, 29 μmol) and **13a** (12.2 mg, 29 μmol) in CH_2Cl_2 (2.6 mL) was treated with TFA (130μL) and stirred at rt in the dark for 5 h. TFA (520 μL) and TMOF (63 μL, 578 μmol) were then added, and the solution was stirred for an additional 16 h. The solvent was removed by rotary evaporation. The residue was redissolved in CH_2Cl_2 and washed with cold, saturated aq $KHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The oil was purified by flash chromatography (silica gel, EtOAc:hexanes = 1:4, 1% NEt_3) to give **15a** (5.1 mg, 34%) as a green film; R_f (1:4 EtOAc/hexanes) 0.30; IR(thin film) 3325, 1730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ -2.52 (br s, 1H), -2.05 (br s, 1H), 2.07 (s, 6H), 3.22 (t, *J* = 8.1, 2H), 3.41 (s, 3H), 3.42 (s, 3H), 3.43 (s, 3H), 3.48 (s, 3H), 3.53 (s, 3H), 3.74 (s, 3H), 3.80 (s, 3H), 4.33 (t, *J* = 7.9, 2H), 4.44 (s, 2H), 8.85 (s, 1H), 9.62 (s, 1H), 9.72 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 11.6, 12.00, 12.02, 16.6, 21.4, 21.9, 32.1, 37.1, 46.0, 52.1, 52.4, 91.1, 97.5, 98.8, 105.3, 128.6, 129.5, 131.5, 133.4, 135.1, 135.3, 136.4, 137.2, 137.4, 138.3, 149.8, 151.8, 162.0, 171.8, 173.9; UV-vis ($CHCl_3$): λ_{max}(ε, $mol^{-1}cm^{-1}$) = 399(151,000), 501 (12,000), 651(42,000) nm; HRMS (EI) Calcd for $C_{32}H_{38}N_4O_2$: 510.2995; found: 510.3002.

Method III: A solution of **12a** (20.3 mg, 58 μmol) and **23** (20.3 mg, 58 μmol) in CH_2Cl_2 (5.5 mL) was cooled to 0°C and treated with TFA (280 μL, 5 v/v%). After stirring for 1h, an additional 1.1 mL (20 v/v%) of TFA was added, the ice bath was removed, and the reaction was stirred at rt for 1.5 h. The solution was cooled to 0°C and quenched with NEt_3 (2.6 mL). The mixture was washed sequentially with water (3 × 5 mL) and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography (silica gel, EtOAc:hexanes = 1:4, 1% NEt_3) to give **15a** (8.3 mg, 28%) as a green solid that was identical to the material prepared by *Method II*.

Method V: A solution of **9a** (16.9 mg, 62 μmol) and **13a** (26.0 mg, 62 μmol) in CH_2Cl_2 (5.7 mL) was treated with TFA (280μL, 5 v/v %) and stirred at rt in the dark for 5 h. More TFA (1.1 mL, 20 v/v %) was then added, and the solution was stirred for an additional 16 h. The solvent was removed by rotary evaporation. The residue was redissolved in CH_2Cl_2 and washed with cold, saturated aq $KHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The product was purified by flash chromatography (silica gel, EtOAc:hexanes = 1:4, 1% NEt_3) to give **15a** (23.5 mg, 74%) as a green film that was identical to the material prepared by *Method II*.

2,2,5,7,8,12, 17,18-octamethylchlorin-13-propionic acid methyl ester (26)

Method IV: A solution of **12a** (12.4 mg, 36 μmol) and **25** (15 mg, 36 μmol) in CH_2Cl_2 (3.3 mL) was cooled to 0°C and treated with TFA (820 μL, 15 v/v%). The mixture was stirred at rt in the dark for 24 h, then cooled to 0°C and quenched with NEt_3 (1.5 mL). The solution was washed sequentially with water (3 × 5 mL) and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography (silica gel, EtOAc:hexanes = 1:4, 1% NEt_3) to give **26** (7.2 mg, 39%) as a green solid, decomp. > 240°C. R_f (3:7 EtOAc/hexanes) 0.49; IR(thin film) 3311, 1731, 1150, 917 cm^{-1}; UV-vis (12% CH_2Cl_2 in MeOH): λ_{max} (ε L mol^{-1} cm^{-1}) = 642 (13000), 591, 501, 358 nm; ^1H NMR (500 MHz, $CDCl_3$) δ -2.43 (br s, 1H), -2.05 (br s, 1H), 2.05 (s, 6H), 3.18 (t, *J* = 8.09, 2H), 3.44 (s, 3H), 3.46 (s, 3H), 2.49 (s, 3H), 3.50 (s, 3H), 3.53 (s, 3H), 3.74 (s, 3H), 3.86 (s, 3H), 4.19 (t, *J* = 8.09, 2H), 4.46 (s, 2H), 8.78 (s, 1H), 9.54 (s, 1H), 9.75 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 11.6, 11.7, 11.9, 12.0, 16.6, 21.5, 22.2, 32.0, 37.5, 46.1, 51.9, 52.3, 90.7, 97.3, 99.3, 105.1, 128.3, 129.6, 131.1, 133.3, 134.9, 135.3, 137.8, 138.29, 138.34, 138.5, 148.9, 150.4, 161.8, 172.3, 174.3. HRMS (EI) Calcd for $C_{32}H_{38}N_4O_2$: 510.2995; found: 510.2993.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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25. Shorter reaction periods were found to be less effective since the final reaction mixtures were invariably contaminated with unidentified pigments that complicated isolation of chlorin. The 5 h reaction time for this step eliminated these pigments.
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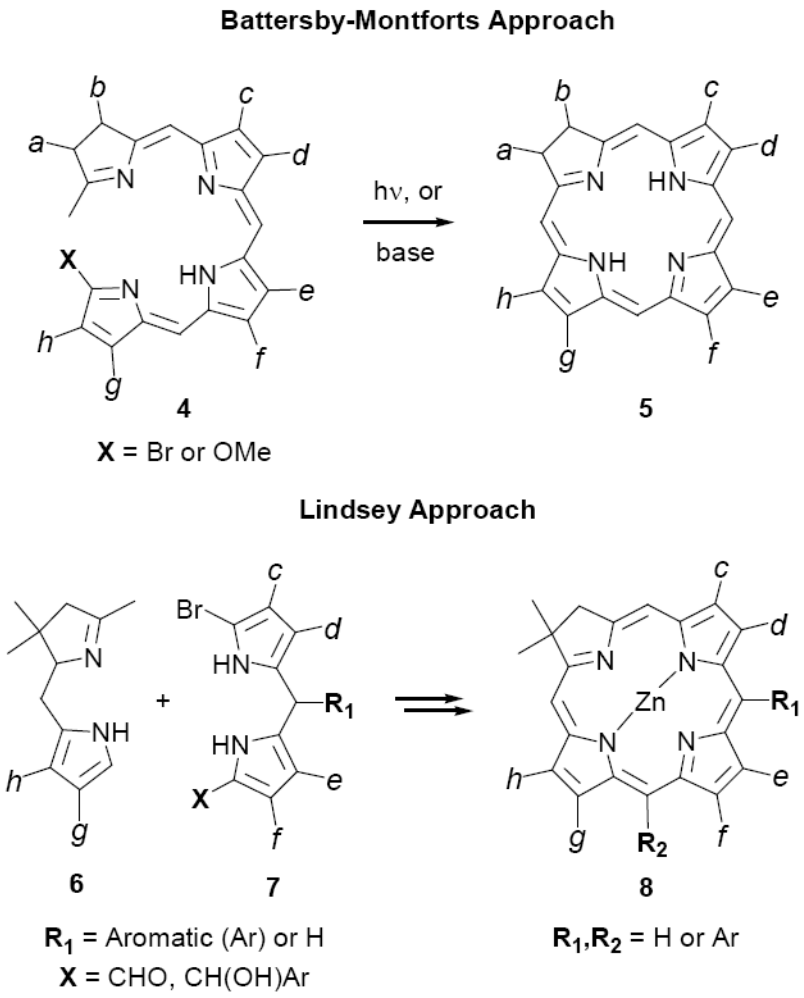
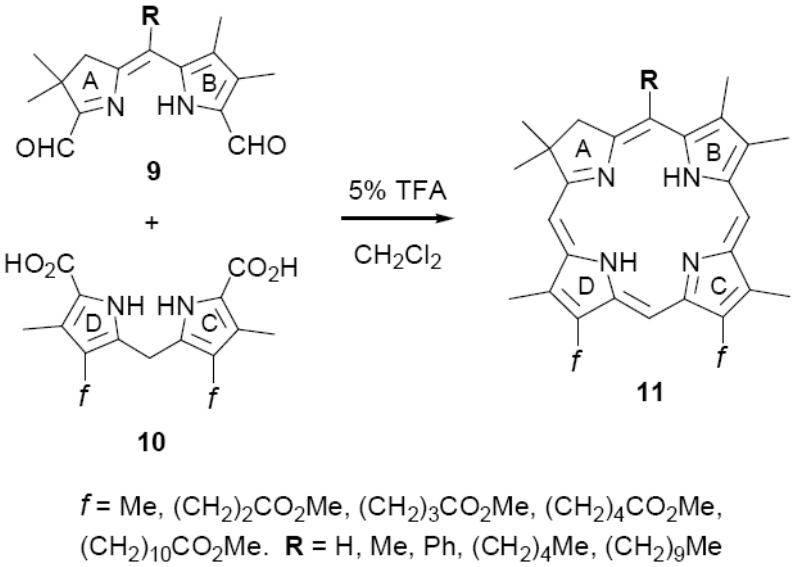
31. Trace amounts of an isomeric chlorin could be detected by UV analysis, but the structure of this compound was not conclusively identified.

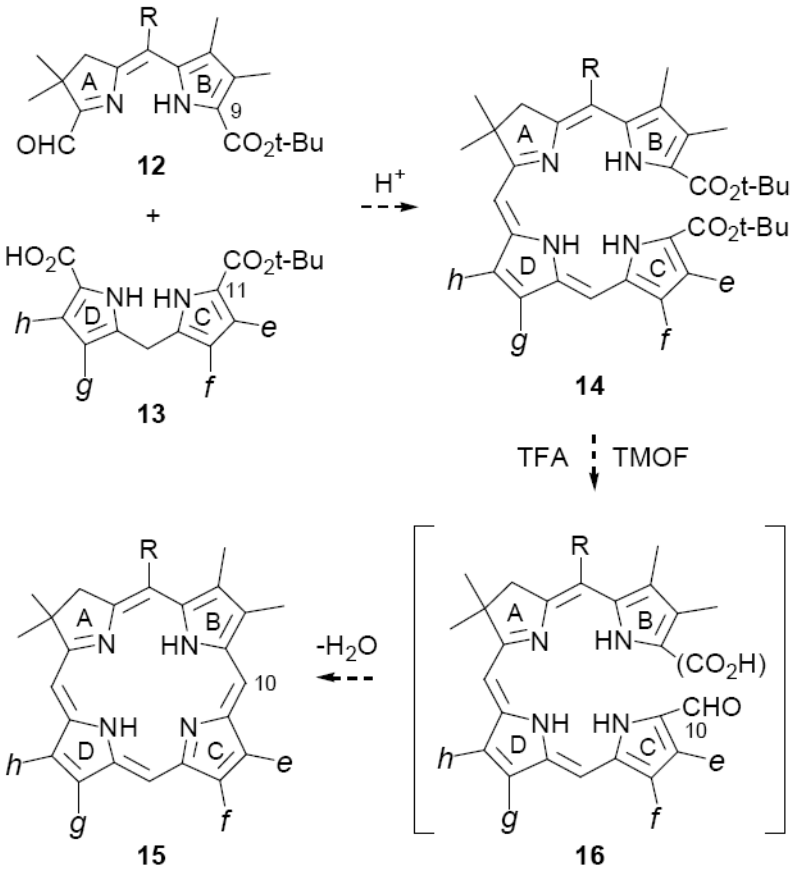


Scheme 1.
Chlorin syntheses by Battersby, Montforts, and Lindsey

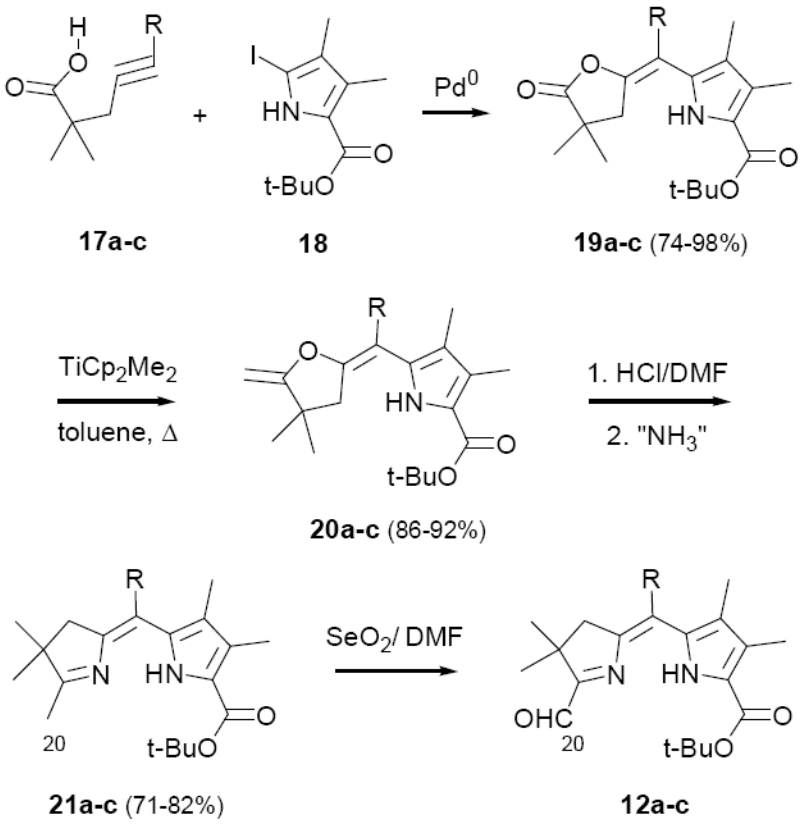


f = Me, $(CH_2)_2CO_2Me$, $(CH_2)_3CO_2Me$, $(CH_2)_4CO_2Me$, $(CH_2)_{10}CO_2Me$. **R** = H, Me, Ph, $(CH_2)_4Me$, $(CH_2)_9Me$

Scheme 2.
Synthesis of C,D-ring symmetric chlorins (*Method I*)

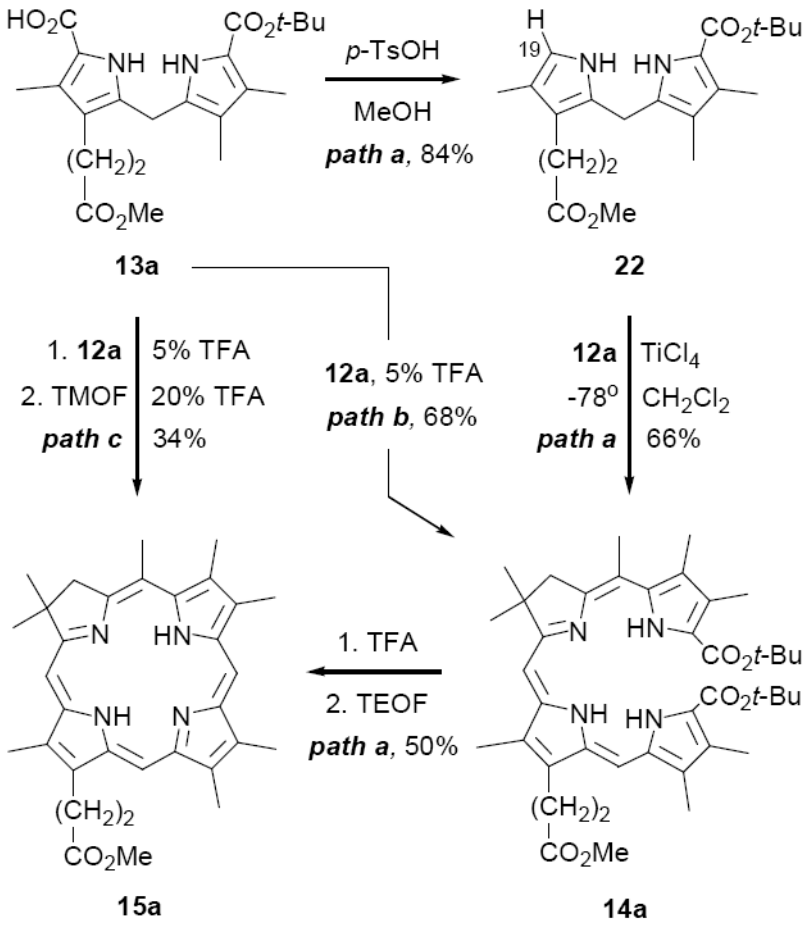


Scheme 3.
Method II for synthesizing unsymmetrical chlorins

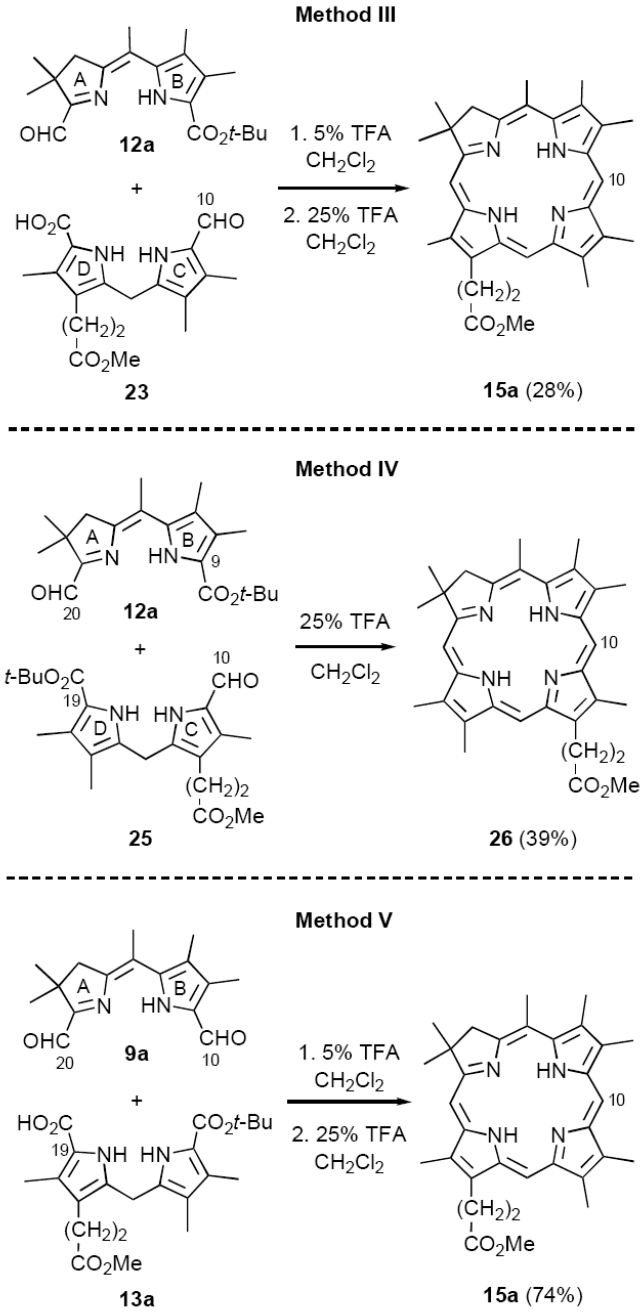


12	R	Yield (%)
a	Me	65
b	Ph	81
c	H	71

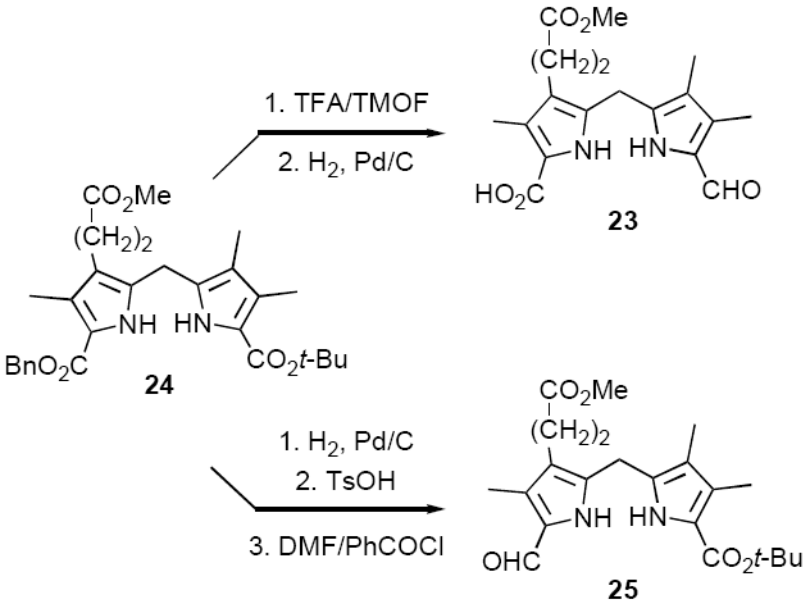
Scheme 4.
Synthesis of A,B-ring precursors **12a-c**



Scheme 5.
Three variations of *Method II; paths a-c*



Scheme 6.
Design and testing of *Methods III-V*



Scheme 7.
Synthesis of C,D-rings **24** and **25** for *Methods III* and *IV*.

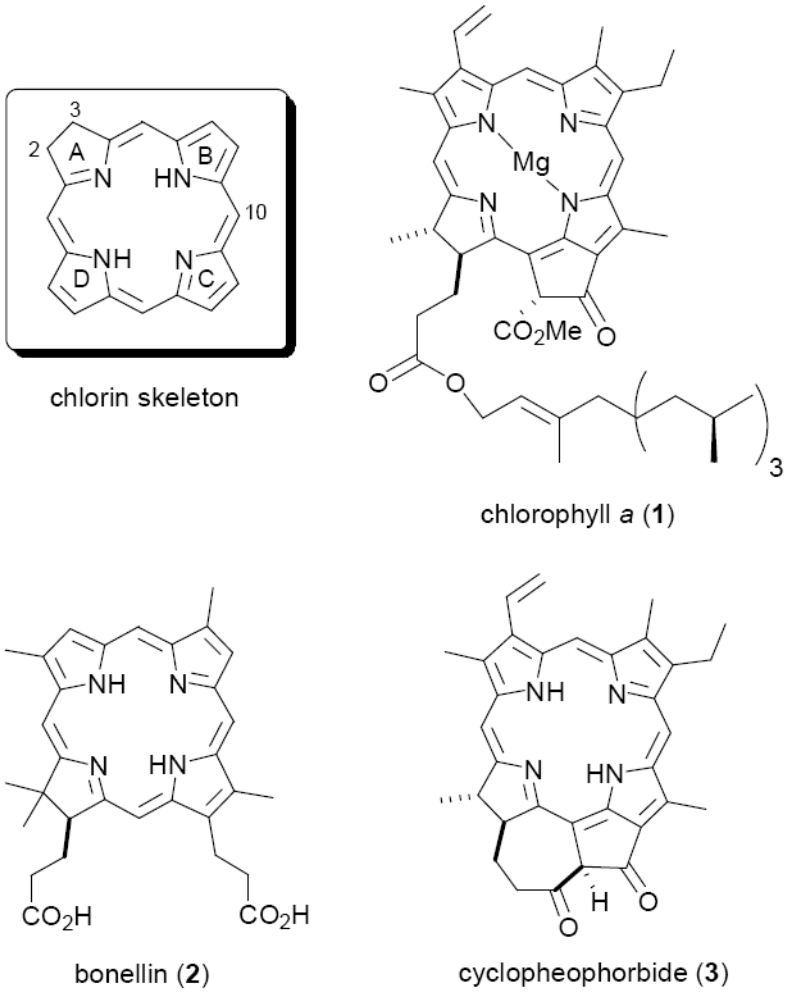
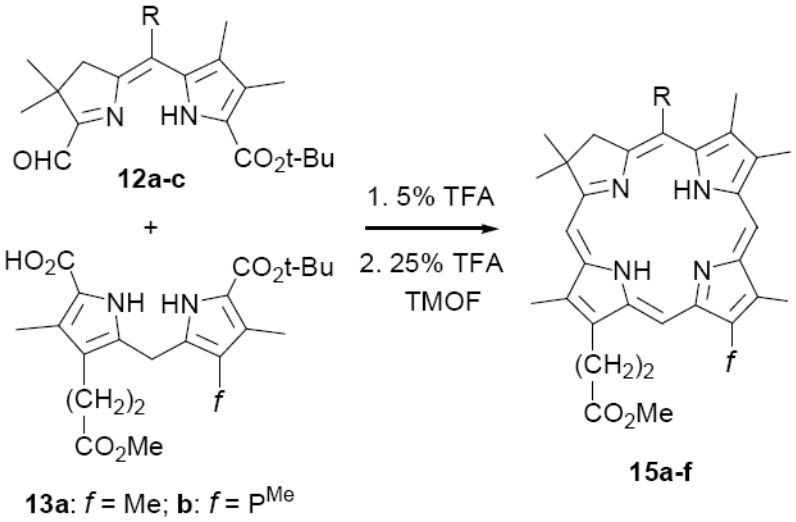


Chart 1.
The chlorin skeleton and some natural chlorins

Table 1

Chlorins prepared by Method *II*



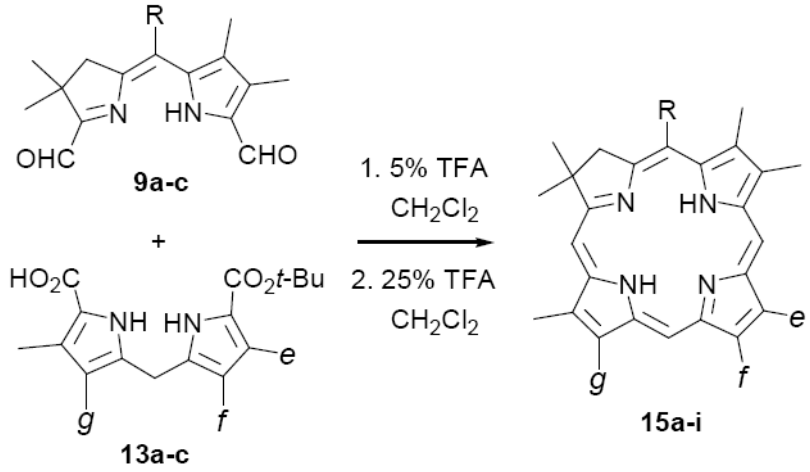
15	Substituents[a]	Yield (%)	Method I Yield (%)[b]
a	*f* = Me; R = Me	38	—
b	*f* = Me; R = Ph	59	—
c	*f* = Me; R = H	11	—
d	*f* = P^{Me}; R = Me	37	73
e	*f* = P^{Me}; R = Ph	38	60
f	*f* = P^{Me}; R = H	12	63

[a] P^{Me} = $CH_2CH_2CO_2Me$.

[b] see reference 21b

Table 2

Chlorins prepared by *Method V*



15	Substituents[a]	Yield (%)	*Method I Yield (%)*[b]
a	*e,f* = Me; *g* = P^{Me}; R = Me	74	—
b	*e,f* = Me; *g* = P^{Me}; R = Ph	87	—
c	*e,f* = Me; *g* = P^{Me}; R = H	39	—
d	*e* = Me; *f,g* = P^{Me}; R = Me	78	73
e	*e* = Me; *f,g* = P^{Me}; R = Ph	73	60
f	*e* = Me; *f,g* = P^{Me}; R = H	38	63
g	*e* = P^{Me}; *f,g* = Me; R = Me	38	—
h	*e* = P^{Me}; *f,g* = Me; R = Ph	77	—
i	*e* = P^{Me}; *f,g* = Me; R = H	22	—

[a] P^{Me} = $CH_2CH_2CO_2Me$.

[b] see reference 21b.